ARIC Manuscript Proposal #1704

PC Reviewed: 10/8/13 **Status: A** **Priority: 2**
SC Reviewed: _____ **Status: _____** **Priority: ____**

1.a. Full Title: Genetic variants identified in genome-wide association studies of dementia and cognitive change in middle age: The Atherosclerosis Risk in Communities (ARIC) study

b. Abbreviated Title (Length 26 characters): AD GWAS SNPs and Cognition

2. Writing Group:

Writing group members: Jan Bressler
David Knopman
Alan Penman
Lisa Wruck
Rebecca Gottesman
Gwen Windham
Thomas H. Mosley
Eric Boerwinkle
Other investigators welcome.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __x___ **[please confirm with your initials electronically or in writing]** JB

F**irst author**: Jan Bressler
Address: Human Genetics Center
UTSCH
1200 Herman Pressler
Houston, TX 77030

Phone: (713) 500-9919 Fax: (713) 500-0900
E-mail: jan.bressler@uth.tmc.edu

Corresponding/senior author (if different from first author correspondence will be sent to both the first author & the corresponding author): Thomas H. Mosley

Address: Department of Internal Medicine
Division of Geriatrics
University of Mississippi Medical Center
2500 N. State Street
Jackson, Mississippi 39216

Phone: (601) 984-6197

E-mail: tmosley @medicine.umsmed.edu

3. Timeline: Statistical analyses: September 2013 – November 2013
Manuscript preparation: December 2013 – February 2014
Manuscript revision: March 2014
Manuscript submission: April 2014

4. Rationale:

Alzheimer's disease is the most common form of dementia[1] and is characterized by significant impairment in memory, behavioral changes, and gradual loss of autonomy. The prevalence of Alzheimer's disease was found to be as high as 20-30% in persons aged 75-84 years, and up to 50% in individuals 85 years of age or older in the large population-based Cardiovascular Health Study.[2] More than 5.3 million Americans are currently estimated to be affected with Alzheimer's disease.[1] When 2,800 subjects who were free of dementia were followed for 29 years in the Framingham Heart Study, the lifetime risk for dementia was reported to be 1 in 5 for women and 1 in 10 for men.[3] Alzheimer's disease was the sixth leading cause of death across all age groups in 2006.[1]

The neuropathological features of Alzheimer's disease are extracellular deposits of plaques composed of β-amyloid peptides and intraneuronal neurofibrillary tangles containing hyperphosphorylated tau. A definitive diagnosis requires examination at autopsy but widely used clinical criteria are summarized in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DMS-IV).[4] Heritability for Alzheimer's disease was estimated to be 58% in a study of 11,884 twin pairs in the Swedish Twin Registry who were 65 years or older[5] but until recently the only genetic variant shown to reproducibly confer an increased risk of common late-onset Alzheimer's disease was the apolipoprotein E4 allele.[6, 7] ARIC was one of the first studies to provide evidence that the processes through which apolipoprotein E (*APOE*) influences the risk for dementia may be initiated many years before clinical diagnosis.[8] When groups of individuals classified into four *APOE* genotype groups were compared (E2/2 + E2/3, E3/3, E4/2 + E4/3, and E4/4), there was increasingly greater cognitive decline across strata from the E2 group to the E4/4 groups in white participants based on tests of both memory and processing speed, and in African-Americans for the test of processing speed.

The current availability of high-density genotyping arrays and the haplotype map of the human genome generated by the International HapMap Project[9] has shifted the focus of genetic studies to genome-wide association analysis of the relationships between large numbers of single nucleotide polymorphisms (SNPs) measured simultaneously and risk for common diseases to identify novel genes influencing a given phenotype. The primary advantage of this analysis strategy is that it does not depend on the *a priori* identification of genes required for the candidate gene approach which is constrained by prior knowledge of statistical association, biological function, or membership in defined pathways. Five novel loci for late-onset Alzheimer's disease (Table 1) have recently been identified in three genome-wide association studies that each included more than 2,000

cases in the study populations examined for gene discovery and all were replicated in at least one independent sample. The aim of this proposal is to determine whether any of these single nucleotide polymorphisms is also associated with cognitive change in middle age in the large biracial population-based ARIC cohort.

db SNP ID	Gene	Chromosome	Reference
rs11136000	*CLU/APOJ*	8	[10, 11]
rs3851179	*PICALM*	11	[10]
rs6656401	*CR1*	1	[11]
rs597668	*EXOC3L2*	19	[12]
rs744373	*BIN1*	2	[12]

Table 1. SNPs identified in genome-wide association studies of AD.

References

1. 2009 Alzheimer's disease facts and figures. Alzheimers Dement 5, 234-70 (2009).
2. Fitzpatrick, A. L. et al. Incidence and prevalence of dementia in the Cardiovascular Health Study. J Am Geriatr Soc 52, 195-204 (2004).
3. Seshadri, S. et al. The lifetime risk of stroke: estimates from the Framingham Study. Stroke 37, 345-50 (2006).
4. Association, A. P. Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, Washington DC, 1994).
5. Gatz, M. et al. Role of genes and environments for explaining Alzheimer disease. Arch Gen Psychiatry 63, 168-74 (2006).
6. Corder, E. H. et al. Gene dose of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. Science 261, 921-3 (1993).
7. Strittmatter, W. J. et al. Apolipoprotein E: high-avidity binding to beta-amyloid and increased frequency of type 4 allele in late-onset familial Alzheimer disease. Proc Natl Acad Sci U S A 90, 1977-81 (1993).
8. Blair, C. K. et al. APOE genotype and cognitive decline in a middle-aged cohort. Neurology 64, 268-76 (2005).
9. The International HapMap Project. Nature 426, 789-96 (2003).
10. Harold, D. et al. Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. Nat Genet 41, 1088-93 (2009).
11. Lambert, J. C. et al. Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. Nat Genet 41, 1094-9 (2009).
12. Seshadri, S. et al. Genome-wide analysis of genetic loci associated with Alzheimer disease. Jama 303, 1832-40 (2010).

5. **Main Hypothesis/Study Questions**:

The aims of the study are:

Aim 1: To estimate the frequency distributions of the test scores for three neurocognitive tests (DWR, DSS, and WF) administered at Visit 2, Visit 4, and at the ARIC Brain MRI

visit in groups of individuals categorized on the basis of genotype for each of the 5 AD-associated SNPs.

Aim 2: To estimate the frequency distributions of the change in test scores for three neurocognitive assessments between Visits 2 and 4 (6-year change), or between Visits 2 and 5 (14-year change) in groups of individuals categorized on the basis of genotype for each of the 5 AD-associated SNPs.

Aim 3: To determine if cognitive status is associated with each of 5 polymorphisms identified in genome-wide association studies of Alzheimer's disease. Cognitive status will be defined by cognitive test scores (DWR, DSS, and WF) at Visit 2, Visit 4, and scores in 5 (factor-derived) cognitive domains assessed at the ARIC Brain MRI Visit (2004-2006).

Aim 4: To determine if change in cognitive function over a 6 or 14-year follow-up period for the DWR, DSS, and WF tests is associated with each of 5 polymorphisms identified in genome-wide association studies of Alzheimer's disease.

Aim 5: To evaluate the possible contribution of gene-gene interaction to interindividual variation in cognition by introducing apolipoprotein E genoypte as well as a multiplicative two way interaction term for AD polymorphism by apolipoprotein E genotype in the analysis models described in Aims 3-4 above.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

Cognitive variables:

The Delayed Word Recall Test (DWR), Digit Symbol Substitution Test (DSS), and Word Fluency Test (WF) are available from Visit 2 (1990-1992, labeled cognitive assessment 1 [CA1], whole cohort), Visit 3 (1993-1995, labeled CA2, Forsyth and Jackson MRI subset), Visit 4 (1996-1998, labeled CA3, whole cohort), and in participants in the ARIC Brain MRI study (2004-2006, labeled CA4, Forsyth and Jackson Brain MRI study subset).

For the subset (N = 1,134) of participants enrolled in the ancillary ARIC Brain MRI study a more extensive battery of neuropsychological tests was administered (2004-2006, CA4). From this battery, 5 domains of cognitive functioning were derived through principal components factor analysis. The factors to be examined in the current study are: (1) Global Mental Status, (2) Memory, (3) Psychomotor Speed, (4) Verbal Fluency, and (5) Executive Function.

Data Analytic Plan:

Caucasian and African-Americans will be evaluated separately by self-reported racial groups. The association of genetic variation and cognition will be analyzed

individually for each of the five SNPs previously associated with Alzheimer's disease in genome-wide association studies. All of the SNPs with the exception of rs744373 have previously been genotyped in the ARIC cohort as part of a collaboration with the Broad Institute to generate genome-wide data for approximately 1,000,000 SNPS using the Affymetrix Human SNP Array 6.0. Analysis of variance (ANOVA) will be performed to assess mean differences in cognitive test scores among individuals with different genotypes. Multiple linear regression will be used to evaluate the association of the Alzheimer's disease-associated SNPs with cognitive scores considered as continuous measures in cross-sectional analyses. Cognitive change will be analyzed as a continuous variable defined as the difference between CA3 test score and CA1 test score (6-year change), or as test score at the ARIC Brain MRI visit – CA1 test score (14-year change) for each of the three cognitive tests. A categorical measurement of cognitive impairment, defined as those falling below the 20^{th} percentile of scores for each of the cognitive tests, will also be analyzed using multivariable logistic regression to predict case status. The analysis of the role of gene-gene interaction between apolipoprotein E alleles and the Alzheimer's disease-associated SNPs in determining cognitive status will be carried out by including interaction terms in the analysis models.

Linear mixed models will also be fit to estimate the effect of the Alzheimer's disease associated SNPs on the rate of change in cognitive function (slope) for the three cognitive tests performed at CA1, CA2, CA3, and CA4. This model assumes that an individual's initial level of cognitive performance (intercept) and rate of change (slope) over time follow those of the population with the exception of random effects that contribute to variability in the intercept and slope. The use of the mixed model accounts for the correlation between cognitive test scores at repeated assessments while also allowing a more precise estimate of the error of variability.

The basic model will consist of terms for the genetic variants, age (years centered at 65 years), sex, education, time in years since baseline, and the interaction of time with the polymorphisms identified in GWAS studies of Alzheimer's disease. The term for time refers to the annual rate of change in cognitive test score in the reference group, and the interaction term reflects the additional effect of the sequence variants on the annual rate of change.

All of the analyses described for Aims 1-5 will be performed by Jan Bressler under the supervision of Eric Boerwinkle; a signed data distribution agreement has been completed.

Inclusion/Exclusion:

We will exclude by DNA restriction, ethnic group (as appropriate to each field center), and missing data. Other exclusion criteria will include history of stroke or TIA prior to Visit 2 and incident stroke. In secondary analyses, we will not analyze those individuals with the lowest 5% of scores on the cognitive tests at CA1 to exclude those with possible preclinical dementia.

Other variables of interest:

In both aims 1 and 2 above, we will determine whether any observed relationships are independent of cardiovascular risk factors and potential confounding factors. These factors will include but are not limited to:

Visit 1- Education, gender, exam center, self-reported race.

Visit 2- Age, *APOE* genotype, fasting blood glucose, history of diabetes, smoking pack years, hypertension status, antihypertensive medications, systolic blood pressure and diastolic pressure, BMI, carotid IMT (right and left sides), alcohol consumption, total cholesterol, LDL-c, HDL-c, triglycerides, Lp(a).

Depression as assessed as Vital Exhaustion at CA1 and the Center for Epidemiological Studies Depression Scale (CES-D) score at CA4. CNS medications (antidepressants, neuroleptics, antianxiolytics, benzodiazepines, antiepileptics) at each visit (CA1, CA2, CA3, CA4).

Incident stroke

Limitations of study:

A limitation of the study is the possibility of selection bias introduced because of differences between those subjects who did and did not participate in the Brain MRI study. To address this issue, baseline characteristics and clinical outcomes will be compared for the two groups.

7.a. Will the data be used for non-CVD analysis in this manuscript? _x_ Yes __ No

b. If Yes, is the author aware that the file ICTDER02 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used? __ Yes _x_ No
(This file ICTDER02 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? __x__ Yes ____ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER02 must be used to exclude those with value RES_DNA = "No use/storage DNA"?
__x__ Yes ____ No

10. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php ___x___ Yes ____ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

#314 Cerebral abnormalities identified on magnetic resonance imaging and cognitive functioning: the ARIC study (Lead author: Thomas Mosley, University of Mississippi, Jackson, MS)

#410 Longitudinal association of alcohol consumption and cognition (Lead author: M Eigenbrodt, University of Mississippi, Jackson, MS)

#672 Changes in cognitive test scores in the ARIC cohort over a 6-year period (Visit 2 to Visit 4) and their correlation with vascular risk factors (Lead author: David Knopman, Mayo Clinic, Rochester, MN)

#924 Apolipoprotein E genotype, cardiovascular risk factors, and cognitive decline in a middle-aged cohort: the Atherosclerosis Risk in Communities Study (Lead author: Cindy K. Blair, University of Minnesota, Minneapolis, MN)

#1010 Omega-3 fatty acids, hypertension, and risk of cognitive decline among older adults: The Atherosclerosis Risk in Communities (ARIC) study (Lead author: May A. Beydoun, University of North Carolina, Chapel Hill NC)
#1018r Physical activity and cognitive decline (Lead author: Patricia M. Dubbert, VA Medical Center, Jackson, MS)

#1066 Metabolic syndrome, diabetes and decline in cognitive function (Lead author: Annie McNeill, GlaxoSmithKline, Research Triangle Park, NC)

#1121 Cognitive change over 12 years and its relationship to cardiovascular risk factors: ARIC-MRI Study (Lead author: David Knopman, Mayo Clinic, Rochester, MN)

#1363 *PCSK9* sequence variation and cognitive decline (Lead author: Jan Bressler, University of Texas Health Science Center at Houston, Houston, TX)

#1153 Association between vascular risk factors and longitudinal changes in ventricular size: a 14 year longitudinal study (Lead author: David Knopman, Mayo Clinic, Rochester, MN)

#1222 The association of microvascular abnormalities with cognitive decline and cognitive status after 10 years (Lead author: Suzanne Lesage, University of Maryland Medical Center, Baltimore, MD)

#1418 Glycemic control (hemoglobin A1c), cognitive decline, and dementia risk: The Atherosclerosis Risk in Communities (ARIC) Study (Lead author: Elizabeth Selvin, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD)

#1858 Midlife occupation and cognitive decline: the ARIC study (Lead author: Mehul D. Patel, University of North Carolina, Chapel Hill, NC)

#1902 The metabolic syndrome, MRI volumetrics and cognitive outcomes: brain structure and function in the ARIC cohort (Lead author: Rebecca F. Gottesman, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD)

#1871 Type 2 diabetes and cognitive decline over 14 years, accounting for mortality (Lead author: Elizabeth Rose Mayeda, University of California, San Francisco, CA)

#1454 The association between cystatin C and cognitive function: The Atherosclerosis Risk in Communities (ARIC) Study (Lead author: Priscilla Auguste, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD)

#1604 The association between hemoglobin and cerebral structure and function (Lead author: Rebecca F. Gottesman, Johns Hopkins Bloomberg School of Public Health, Baltimore MD)

#1739 Atrial fibrillation is associated with cognitive decline and brain MRI abnormalities: The ARIC study (Lead author: Lin Y. Chen, University of Minnesota Medical School, Minneapolis, MN)

#1742 Education and cognitive change from 1990-92 to 2004-06 (Lead author: Rebecca F. Gottesman, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD)

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? __x__ Yes ____ No

11.b. If yes, is the proposal

_x_ A. primarily the result of an ancillary study (list number* AS#_1999.01)

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____)

*ancillary studies are listed by number at http://www.cscc.unc.edu/aric/forms/

12. **Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.** Agree**.**